Appl. No. 09/806,552 Amdt. dated August 17, 2005 Amendment under 37 CFR 1.116 Expedited Procedure Examining Group 1638

### REMARKS/ARGUMENTS

### I. Status of the Claims

Claims 1-24 are pending. Claims 15-24 are withdrawn from consideration.

### II. The Office Action

The Action rejects the claims on a variety of grounds. Applicants traverse. The rejections are discussed below in the order in which they are presented in the Action.

## A. Rejection for lack of written description

The Action maintains the rejection of claims 1-14 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. The Action asserts that the claims contain subject matter that was not described in the specification so as to reasonably convey to the practitioner that, at the time the invention was made, the applicant had possession of the claimed invention. In response to the Applicants' argument that the art provided persons of skill in the art with numerous inhibitors of farnesyltransferase, and that it was unnecessary to set forth in the specification information that would be known to persons of skill in the art as of the filing date, the Action states that the claims are not drawn to inhibitors of farnesyltransferase per se, but to methods of inhibiting farnesyltransferase by transforming a plant with an expression cassette comprising a nucleic acid sequence encoding a farnesyltransferase inhibitor. The Action states that neither the specification nor the prior art describe nucleic acid sequences encoding proteins whose expression would inhibit farnesyltransferase in a plant transformed therewith. According to the Action, Reiss et al., Cell 62:81-88 (1990) (hereafter, "Reiss") and Tamanoi, TIBS 18:349-353 (1993) (hereafter, "Tamanoi"), cited by the prior Office Action, dated January 30, 2004, teach only farnesyltransferase inhibitors that will inhibit farnesyltransferase in vitro or in mammalian in vivo systems, but do not refer to farnesyltransferase inhibitors that would function to inhibit farnesyltransferase when expressed in plant cells. Applicants traverse.

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Applicants pointed out in their Request for Reconsideration filed in July 2004, literally scores of peptide and peptidomimetic inhibitors of farnesyltransferase (sometimes hereafter referred to as "FTase") were known before the priority date of the application, including not only those taught in Reiss and Tamanoi, but also peptides and peptidomimetics taught in a number of patents which had issued before the priority date (such as U.S. Patent No. 5,856,310, which teaches the peptide KKSKTKCVIM) and which were incorporated by reference into the specification. Further, promoters that would drive expression specifically in plant guard cells were known in the art, as recited in the present specification at page 15, lines 24-29. The July 2004 Request therefore pointed out that the Applicants, like everyone else in the art as of the priority date, had in their hands possession of a large number of inhibitors of farnesyltransferase at the time of filing, and noted that it was unnecessary to recite specific nucleic acid sequences in the specification merely to show that they also had a copy of the standard genetic code and could convert the peptide sequences into corresponding nucleic sequences that would encode them. Thus, Applicants respectfully submitted that the written description rejection had to be reconsidered and rejected on this basis alone.

The current Action now seems to agree that these various references teach farnesyltransferase inhibitors. But it argues, as noted above, that "Neither the specification nor the prior art describe nucleic acid sequences encoding proteins whose expression would inhibit farnesyltransferase in a plant transformed therewith, i.e., inhibitors of farnesyltransferase that would function to inhibit farnesyltransferase in a plant upon expression in vivo." Action, at page 3.

The concern expressed by the Action, therefore, is not that the nucleic acid promoter sequences taught by the references cited by (and incorporated into) the specification are somehow not taught, or that the various inhibitors known in the art as of the priority date (and referenced in the specification) needed to be set forth in the specification before it could be agreed that the Applicants had the invention in hand, but that the inhibitors known in the art would not work to inhibit farmesyltransferase when expressed in plants. This is, of course, different from saying that the Applicants needed to describe a specific sequence to show they

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had the invention in hand. Applicants respectfully submit that the Action thus concedes that the question is whether the invention works as claimed, not whether the applicants have described a sequence showing possession of the invention. The rejection is therefore properly considered as one for alleged lack of utility, not one for lack of written description.

As noted, the Action's states that the teachings pointed to by the Applicants concern only "inhibitors of farnesyltransferase that are known to inhibit farnesyltransferase in vitro or nonplant, e.g., mammalian, in vivo systems, they make no reference to farnesyltransferase inhibitors that would function to inhibit farnesyltransferase in plants."

Action, at pages 3-4, bridging paragraph. Applicants respectfully observe, however, that the specification states "The homology of the farnesyltransferase gene family and the fact that plant FTase can be substituted for endogenous FTase in FTase-deficient yeast [citation omitted] lead us to expect that farnesyltransferase inhibitors effective in one organism will have an inhibitory effect on FTases of other organisms." Specification, at page 15, lines 10-14. Applicants respectfully note that the Action's rejection of the expectation stated in the specification is not grounded on any art supported reference or statement of knowledge by the Examiner and, in contrast to the statement in the specification, is entirely unsupported. And, in fact, the evidence in the art is to the contrary.

In arguing that FTase that inhibit mammalian FTases would not necessarily have the same effect on plant FTases, the Action attempts to draw a distinction between the farnesyltransferases of plants and of mammals. Applicants respectfully note, however, that it was known before the priority date that inhibitors of mammalian farnesyltransferase also inhibit plant farnesyltransferase. In this regard, Qian et al., Plant Cell, 8(12):2381-2394 (1996) showed that manumycin, a FTase inhibitor used to study FTase function in yeast and mammals, also completely blocked *in vivo* protein farnesylation in pea plant cells. See, Qian et al. at page 2386, left column, last full paragraph and right column, lines 5-9. (A copy of Qian et al. is enclosed for the Examiner's convenience.)

With the recent amendment of the rules to include Rule 1.116(e), the consideration of additional evidence requires a showing of good and sufficient reasons why the

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affidavit or other evidence is necessary and was not earlier presented. The Qian et al. reference, and the others submitted in connection with the discussion in this section, are necessary because the Examiner has maintained her rejection over the Applicants previous explanations on the same point. The evidence being presented therefore corroborates factual positions which have been previously presented. The evidence was not presented earlier because it was believed that the specification and argument presented were sufficient to overcome the previous Action's unsupported contentions. It is hoped that the Examiner's review of the present evidence of what was known in the art prior to the priority of the present specification will narrow or overcome the issues in dispute or simplify the issues for appeal.

Returning to the substance of the discussion, the Action's thesis that FTase inhibitors that inhibit mammalian FTase might not also inhibit plant FTase is thus directly rebutted by Qian et al. For extra measure, it is also noted that the art taught, before the priority date, that FTases of organisms as different as yeast and mammals are similar both structurally and functionally (see, e.g., Gomez et al., "Purified yeast protein farnesyltransferase is structurally and functionally similar to its mammalian counterpart" Biochem J. 289:25-31 (1993) (abstract attached)), and that plant FTases resemble mammalian and yeast FTases, and were specifically cross-reactive in Western blots with antibodies to mammalian FTase. See, e.g., Parmryd et al., "Identification of spinach farnesyl protein transferase" Eur J Biochem. 234(3):723-31 (1995) (abstract attached).

Applicants respectfully call the Examiner's attention to MPEP §2107.02 III(A), which instructs the examining corps on how to treat assertions of utility. Section 2107.02 III(A) cites *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971), which it quotes as follows:

"[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented <u>must</u> be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is

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reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. (emphasis added)."

Section 2107.02 continues with the following instructions to the examining corps:

Thus, Langer and subsequent cases direct the Office to presume that a statement of utility made by an applicant is true . . . any inquiry must start by asking if there is any reason to question the truth of the statement of utility. . . If the asserted utility is credible (i.e., believable based on the record or the nature of the invention), a rejection based on "lack of utility" is not appropriate. Clearly, Office personnel should not begin an evaluation of utility by assuming that an asserted utility is likely to be false, based on the technical field of the invention or for other general reasons.

## Id. (Emphasis added).

Applicants respectfully submit that the rejection posed by the Action is a utility rejection - will the farnesyltransferase inhibitors known in the art work to inhibit farnesyltransferase when expressed in plants - rather than a written description rejection. As also noted above, the specification indicates that both the homology in the FTase gene family and the fact that plant FTase works in yeast create a presumption that FTase inhibitors effective in one organism will have an inhibitory effect on FTases of other organisms. Under §2107.02, the burden is on the Action to present reasons to doubt the objective truth of the statements in the specification. The Action does not do so. Moreover, the Gomez and Qian references cited above show that the art was aware before the priority date that plant, yeast, and mammalian FTase in fact not only share structural and functional features, but also that an inhibitor of yeast and mammalian FTases also inhibited plant FTase, findings which further support the that an inhibitor of a mammalian FTase will also inhibit plant FTase. In contrast, the Action provides no art-supported reference or indication of personal knowledge on the part of the Examiner indicating that inhibitors of mammalian FTases will not also inhibit a plant FTase. The Action offers only speculation, which has been rebutted by the references cited herein.

In short, the "written description" rejection in the Action is an argument that the various inhibitors of farnesyltransferase cited in the specification are known to "inhibit

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farnesyltransferase in vitro or nonplant, e.g., mammalian, in vivo systems, [it makes] no reference to farnesyltransferase inhibitors that would function to inhibit farnesyltransferase in plants." Action, at pages 3-4, bridging paragraph. But, as shown above, it was known in the art that inhibitors of yeast and mammalian farnesyltransferases could also inhibit plant farnesyltransferase. Applicants respectfully submit that the Examiner has not met the burden set by MPEP §2107.02 and that the assumption underlying the rejection is contradicted by the teachings in the art.

Reconsideration and withdrawal of the rejection are respectfully requested in light of the above remarks.

## B. Rejection for lack of enablement

The Action maintains the rejection of claims 1-14 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement. The Action asserts that the claims contain subject matter that was not described in the specification so as to enable one of skill in the art to make and use the invention. The Action maintains that the rejection is not predicted on the unpredictability of farnesyltransferase inhibitors generally (Action, at page 5), or expression of farnesyltransferase inhibitors in general (id.), but on the expression of farnesyltransferase inhibitors in a plant. (Id.) The Action then addresses the various Wands factors in particular. Applicants traverse.

In response to the Action, Applicants provide herewith the Declaration of Dr. Judy Callis (the "Declaration"). Dr. Callis is a full professor at the University of California, Davis and holds an endowed chair in Plant Biochemistry. She is an author of some 50 scientific publications on plant biochemistry and is knowledgeable about the expression of proteins in transgenic plants, as reflected in part by the fact she is a co-inventor on several patents, U.S. Patent Nos. 5,773,705 and 6,222,095, which employ the expression of proteins in transgenic plants. She is on the editorial board of the Journal of Plant Physiology, is Monitoring Editor of the journal Plant Physiology, and has also served as an ad hoc reviewer for The Plant Journal,

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Plant Cell Reports, Planta, and Plant Science. A copy of her c.v. accompanies her Declaration. She is not an inventor of the subject application and has no financial interest in it.

With the recent amendment of the rules to include Rule 1.116(e), the consideration of additional evidence requires a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. The Declaration is necessary because the Examiner has simply dismissed Applicants' previous explanations regarding the enablement of the invention. The evidence being presented corroborates factual positions which have been previously presented to the Examiner. The declaration was not presented earlier because the undersigned believed the information set forth in the previous request for reconsideration was sufficient to overcome the unsupported assertions of the previous Action. It is hoped that the Examiner's review of the declaration will narrow or overcome the issues in dispute or simplify the issues for appeal.

According to the Action, the enablement rejection is "predicated on the failure of the specification to provide sufficient guidance with respect to which particular farnesyltransferase inhibitor to express and with respect to how to express that farnesyltransferase inhibitor at concentration[s] effective to confer a useful phenotype to a transgenic plant, in view of what the prior art teaches with respect to farnesyltransferase inhibitors." Action, at page 7. The Action further states that, while it does not dispute that the level of skill in the art is very high, this "does not compensate for the lack of guidance provided by the specification with respect to which particular farnesyltransferase inhibitor to express, and with respect to how to express that farnesyltransferase inhibitor at concentration[s] effective to confer a useful phenotype on a transgenic plant." Action, at age 8.

Dr. Callis was asked to consider the Action's contentions in light of what would have known to a person of skill as of the September 2001, priority date. In her Declaration, Dr. Callis states

"As the specification observes, a number of farnesyltransferase inhibitors were known as of the filing date. The Action's point seems to be in part that the person of skill would be at a loss as to how to proceed without a teaching of which specific inhibitor to choose.

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With respect, I would not expect anyone who has created transgenic plants to need more explanation of how to proceed than is provided in the specification. The process would in fact be straightforward. For expression in transgenic plants, persons of skill would select a protein since it is a central dogma of modern biology that genes encode proteins. The choice of the particular inhibitor protein to express would be largely a matter of convenience, based on whether any expression cassettes encoding farnesyltransferase inhibitors could be purchased from laboratory supply houses, borrowed from a colleague, or readily cloned."

### Declaration, at ¶8.

### Dr. Callis further states:

"I am aware that the specification notes that promoters are known that drive expression of constructs specifically in guard cells. Knowledge of how to construct an expression cassette coupling a cell type-specific promoter and a gene of interest is widely available in the art. I also understand that the specification summarizes how to construct a recombinant vector and how to transform a plant to express the transgene. Accordingly, in view of the knowledge in the art and the skill level of its practitioners, I believe the specification contains all the teachings necessary to enable persons of skill to produce plants exhibiting inhibition of farnesyltransferase activity in their guard cells and therefore, according to the teachings of the specification, with decreased transpiration."

Callis Declaration, at ¶9. Thus, contrary to the Action's unsupported assertions, Dr. Callis, as a person of skill in the art considers that she would be enabled to produce plants expressing FTase inhibitors.

In response to the enablement rejection of the first Office Action, Applicants pointed out that the specification taught the expression specifically in guard cells of a  $\beta$ -glucoronidase (GUS) reporter gene driven by a guard cell-specific promoter. The current Action dismisses the working example as irrelevant. The Action notes that the claims are not directed to expression of a GUS reporter gene, and states that the GUS protein product "is not know[n] or

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disclosed as being equivalent in function or effect to the protein product expressed by the claimed plants." Action, at page 10.

Dr. Callis states that the Action's contentions are contrary to what would be understood by persons of skill in the art. Specifically, she states:

"Based on my training and experience in expressing recombinant proteins in transgenic plants, I believe the Action's contentions are incorrect, and would be known to be incorrect by persons of skill in this art. The Action is of course correct that GUS is "not known or disclosed as being equivalent in function or effect" to a farnesyltransferase inhibitor. GUS was, however, not supposed to have a function or effect equivalent to that of a farnesyltransferase inhibitor in the study reported — I and others in the art are aware that GUS is a reporter protein used to show whether an expression cassette results in the expression of a transgene in a desired cellular location and, where appropriate, at a desired point of development. The results reported indicate that the GUS transgene was expressed in the desired cellular location. Thus, the Action's statement that GUS is not shown to be "known or disclosed as being equivalent in function or effect" to a farnesyltransferase inhibitor is a *non sequitor* and ignores what the expression of GUS reported in the specification would evidence to persons of skill in the art."

# Callis Declaration, at ¶11.

She further declares:

"What the expression of GUS reported in the specification shows to me, and would show to others of skill in the art, is that the expression of the GUS transgene could be driven in guard cells, the desired cellular location, by the expression cassette used. To the person of skill in this art, this raises the expectation that other proteins, such as a farnesyltransferase inhibitor, can likewise be expressed in a very specific manner in guard cells by substituting the coding sequence for the inhibitor for the sequence encoding GUS used in the experiment reported.

Callis Declaration, at ¶12.

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She then notes that there have been some difficulties in expressing proteins in plants:

Most coding regions from transgenes will be expressed at levels that can inhibit endogenous activities. There is of course no guarantee that the level of expression will be high in any given plant. Some genes have proven difficult to express in plants, and there are a number of things that could cause problems in expression, such as the presence of a cryptic splice site, instability of RNA transcribed from the expression cassette, causing its rapid degradation, incorrect codon usage resulting in low translation levels, silencing of the transgene so that it does not continue to express, rapid degradation of the expressed protein, resulting in low endogenous levels and, finally, integration of the transgene in a site that inhibits or blocks transcription.

Callis Declaration, at ¶13.

She declares, however, that the practitioner can usually readily overcome these issues:

Each of these issues can, however, usually be solved by changing nucleic acid sequence of the transgene and/or screening through a number of transgenic plants to find one with high expression. Someone skilled in the art would know that these factors could influence transgene expression and make the necessary alterations. While considerable work might be required (assuming one of the problems mentioned in the preceding paragraph was in fact present), that amount of experimentation is routine in the art when expressing transgenes in plants.

Id., at ¶14.

The Action further states that expression of a FTase in a plant is "unpredictable because expression methods must be specifically adapted in order to achieve a particular desired phenotype, as different levels of protein expression produce different phenotypes, because farnesyltransferase inhibition is dependent on inhibitor concentration and further varies between different types of farnesyltransferase inhibitors and because compounds that inhibit

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farnesyltransferase in vitro may be unstable in vivo." Action, at pages 10-11, bridging paragraph. In response, Dr. Callis states:

"there is usually at least some expression of the transgene. And, even if, for example, the protein product was rapidly degraded, the continuing production of fresh protein would likely have some effect on farnesylation in the cell. Thus, and contrary to the Action's analysis, I would expect with a reasonable expectation of success that if I replaced the region coding for GUS with a region coding for a farnesyltransferase inhibitor in the expression cassette used in the study reported in the specification, I would get at least some expression of the farnesyltransferase inhibitor in those cells, and that that expression would have at least some effect on farnesylation in the cell. I do not understand the claims to require any particular amount of inhibition of farnesyltransferase."

Callis Declaration, at ¶15.

With respect to the Action's contention about the alleged instability of FTases in plant cells *in vivo*, she notes that practitioners would generally produce a group of transgenic plants, and that: "I would expect that for at least some of the plants, the continuing production of fresh farnesyltransferase inhibitor would maintain the effect of inhibiting farnesyltransferase activity below that which would be present in the absence of the inhibitor." Callis Declaration, at \$\frac{1}{2}\$1.

The Action further maintains that the amount of experimentation necessary to make and use the invention is undue, due to the alleged "unpredictability of the effect of expressing a nucleic acid encoding a farnesyltransferase inhibitor in a plant, the lack of guidance with respect to which particular farnesyltransferase inhibitor to express, and the lack of guidance with respect to how to express that farnesyltransferase inhibitor at concentration[s] effective to confer a useful phenotype on a transgenic plant." Action, at pages 11-12.

Dr. Callis addresses this argument as follows:

"The Action's argument seems to me to prove too much. Persons of skill in this art expect that there are always some variations in expression levels between transgenic

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plants, even plants made following identical procedures. Even the most detailed teaching in the specification showing the production of a transgenic plant expressing a farnesyltransferase inhibitor with reduced transpiration, therefore, would not permit the practitioner to uniformly produce plants with identical phenotypes. For this reason, practitioners generate a multitude of transgenic plants, select for those that express the transgene, select further for those that express the desired phenotype, and then reproduce those plants asexually or sexually to scale up the number of plants. It is understood by practitioners that it cannot be predicted with any degree of certainty before testing that any particular plant will express a desired transgene at a given level, but it can generally be predicted that a group of transgenic plants will have differences in levels of the transgene and that at least some will express the transgene at phenotypically relevant levels. This degree of experimentation is considered routine in the art. In contrast, under the standard set forth in the Action, no teaching in the specification would be sufficient because it could not teach how to produce plants which always have the same phenotype.

Callis Declaration, at ¶17. Thus, Dr. Callis, a person of skill in this art states that the experimentation necessary to practice the invention is the degree of experimentation considered routine in this art. Applicants respectfully remind the Examiner that MPEP 2164.06 reminds the examining corps that *In re Wands* itself states "a considerable amount of experimentation is permissible, if it is merely routine." *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)) (emphasis added).

Dr. Callis has hands on experience, is widely familiar with the scientific literature - as evidenced by her activities as an editor and reviewer on a number of important journals in the field - and has trained a number of graduate students in plant science. Applicants therefore respectfully submit that Dr. Callis's judgment as to what constitutes routine experimentation in the art is entitled to considerable deference. In contrast, the standard set by the Action is not only unsupported, but is also internally inconsistent since, even if the specification showed the

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production of a plant expressing a FTase inhibitor at a given concentration, it would only show the practitioner that it could be done, not how to do so uniformly.

The Action further maintains that the "grounds of unpredictability alleged in the prior office action with respect to the potential in vivo instability of farnesyltransferase inhibitors is applicable . . . a distinction need not be made between the intracellular or extracellular location of expressed farnesyltransferase inhibitors, as it is the products produced by the cells themselves which are secreted into the extracellular environment which affect the activity of farnesyltransferase inhibitors. Accordingly, the farnesyltransferase inhibitors . . . expressed within cells need not be exposed to extracellular fluids in order to potentially be affected by products that are produced by the cells themselves." Action, at page 14.

Dr. Callis specifically addresses this contention, as follows:

"I want to address specifically the Action's contention that proteases found in the systemic circulation in mammals are made within the cell and therefore available to degrade farnesyltransferase inhibitors within the cell. This contention ignores the fact that proteins to be secreted from the cell are typically synthesized with a leader sequence that marks the protein for transport to the cell's exterior, where the leader sequence is typically cleaved to produce the active form of the protein. Proteins with these leader sequences are never present in the cell cytosol in an active form. Thus, the fact that there are proteases in the systemic circulation in mammals does not suggest to me as a person of skill that the proteases are also present in the cytosol of the mammalian cells producing them. It further does not suggest to me that such proteases would be present in the cytosol of plant cells, even assuming that plant cells produce such proteases. There is no evidence provided by the Action that proteases would be available within the cell cytosol to degrade a farnesyltransferase inhibitor expressed within the cell. Accordingly, I do not believe that the Action's contentions regarding the possible instability of farnesyltransferase inhibitors or the possible existence of proteases for farnesyltransferase inhibitors within plant cells would affect the ability of the practitioner to reach and

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sustain phenotypically relevant levels of farnesyltransferase inhibitor expression in transgenic plants.

Callis Declaration, at ¶22. In considering Dr. Callis's comments, it should be noted that the list of Dr. Callis's publications in her c.v. shows she is an authority on the labeling of proteins for destruction and on protein trafficking in plant cells. Her comments on whether endogenous proteases would cause degradation of FTases within cells are therefore worthy of considerable deference.

In sum, it is respectfully submitted that the Action's contentions regarding the alleged unpredictability of the expression of FTase inhibitors in plants, and the alleged instability of FTase inhibitors once expressed are generally unsupported and, to the extent they are supported, are contradicted by the Callis Declaration. Applicants respectfully request reconsideration of the Action's contentions in light of the Declaration and the remarks herein, and withdrawal of the rejection.

### CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, she is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted

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